S M & RC PROTOCOL

1-PATIENT ENROLLEMENT

2-EVALUATION PERFORMA

3-WORK UP

4-NEONATAL SEIZURES -MANAGEMENT PROTOCOL

5-NEONATAL STATUS EPILEPTICUS -MANAGEMENT PROTOCOL

6-BRIGHTON COLLABORATION NEONATAL SEIZURES CLASSIFICATION

7-PATIENT MANAGEMENT CHART (increase extra page)

8-2021-ILAE NEONATAL SEIZURES CLASSIFICATION

9-SEIZURES ETIOLOGY

10-SEIZURES RISK FACTORS

11-ANTI SEIZURES DRUGS

12-DEFINITIONS

STAR MEDICAL & RESEARCH CENTER

NEONATAL SEIZURES PROTOCOL

1. IF A NEONATE IS SUSPECTED TO HAVE SEIZURE, WE ENROLL THE PATIENT
2. WE MEASURE VITAL SIGNS & RECORD GROWTH PARAMETERS
3. IF PATIENT IS STABLE WE EVALUATE THE PATIENT USING EVALUATION PERFORMA
4. WE CLASSIFY THE SEIZURE USING BRIGHTON COLLABORATION SCHEMA
5. WE MANAGE PATIENT WITH ASM IF THE SEIZURE LEVEL OF CERTAINITY FALLS IN 1,2,OR 3.
6. IF PATIENT IS UNSTABLE WE FIRST STABILIZE THE PATIENT, THEN DECIDE IF PATIENT IS IN STATUS EPILEPTICUS
7. IF PATIENT IS IN STATUS EPILEPTICUS WE MANAGE AS MENTIONED AGAINST STATUS EPILEPTICUS PROTOCOL
8. WE ASSUME ALL NEONATAL SEIZURE AS PROVOKED FOCAL SEIZURES UNLESS PROVED OTHERWISE
9. WE MANAGE NEONATAL SEIZURES AS MENTIONED AGAINST NEONATAL SEIZURES MANAGEMENT PROTOCOL
10. WE KEEP RECORD IN PATIENT MANAGEMENT CHART
11. WE KEEP SEIZURE LOG
12. WE SUMMARIES THE CASE IF NEONATE AGE EXCEEDS 28 DAYS, LOST TO FOLLOW UP OR EXPIRED

EVALUATION PERFORMA

1- MATERNAL MEDICAL CONDITION...

2- MATERNAL TORCH SCREEN STATUS...

3- MATERNAL HBV,HCV STATUS...

4- MATERNAL PARITY:...

5- PREGNANCY DATING: 1-SCAN...2-LMP...

6- GESTATIONAL AGE..

7- PLACE OF DELIVERY:..

8- MODE OF DELIVERY:..

9- BIRTH WEIGHT:...

10- APGAR SCORE @ 1-MINUTE...@ 5-MINUTES...

11- NUMBER OF SEIZURES:...

12- TYPE OF SEIZURE:..

13- DURATION OF SEIZURING:..

14- FEVER DURING SEIZURING:..

15- FAMILY HISTORY OF : 1-SEIZURE DISORDER..............................2-BLEEDING DISORDER.................................

3-COAGULATION DISORDER:...

16- PHYSICAL EXAM; FINDINGS: AF:....................DYSMORPHYSIM:....................MICROCEPHALY:...................

MACROCEPHALY:.......................................NEUROCUTANEOUS STIGMATA:...

17- INVESTIGATIONS AVAILABLE

1-LAB TESTS 2-EEG 3-USS-BRAIN 4-CT SCAN BRAIN 5-MRI BRAIN

6-CT/MR VENOGRAPHY 7-GENETIC TESTING

18- PROBABLE

1-SEIZURE @ YES @ NO 2-PROVOKED @YES @ NO

3-CAUSE..@ NOT SURE

WORK UP

1.BASIC WORK UP

1.SERUM SODIUD 2. SERUM CALCIUM 3. BLOOD SUGAR 4. ULTRASOUND BRAIN

5. cEEG 6. LP

2. ADVACE WORK UP

I-BLOOD

1- SERUM MAGNESIUM

2- SERUM PHOSPORUS

3- SERUM AMMONIA

4- SERUM LACTATE

5- SERUM PYRUVATE

6- ABGs

7- PLASMA AMINOACIDS LEVEL

8- PLASMA VERY LONG CHAIN FATTY ACIDS LEVEL

9- TORCH PANEL ASSAY

10- SERUM ACEYL CARNITINE PROFILE

II-URINE

1. URINE ORGANIC ACIDS

III-CSF

1. CSF LACTATE
2. CSF PYRUVATE
3. CSF GLYCINE
4. CSF HERPES PCR

IMAGING

1. CONTRAST-ENHANCED MRI BRAIN WITH EPILEPSY PROTOCOL
2. CT SCAN-PLAN
3. MR/CT VENOGRAPHY
4. VIDEO-EEG

TABLE-1

WORK UP FOR ACUTE PROVOKED NEONATAL SEIZURES				
URGENT EVALUATION	***SUSPECTED HIE***	***SUSPECTED INFECTION***	***SUSPECTED STROKE***	***SUSPECTED METABOLIC DISORDER***
Check blood glucose, electrolytes, cbc & confirm with EEG	Check birth hx & APGAR score, screen for other causes depending on clinical scenario; assess need for therapeutic hypothermia	Obtain blood cultures & TORCH Titers; CSF studies: glucose & proteins, cell counts, culture, PCR assay for HSV. Consider pathological assessment of placenta	IMAGING: USS brain, CT scan brain, MRI brain with diffuse weighted imaging FIND CAUSE: Thrombophilia, vascular or cardiac cause? Consider Echo & pathological assessment of placenta	SCREEN for metabolic abnormalities: plasma ammonia & lactate, serum pyruvate, aminoacides, very long chain fatty acides, urine organic acides, biotinidase, pipecolic acide, pyridoxine, pyridoxal-5 phosphate. Consider ophthalmologic assessment.

NEONATAL SEIZURE MANAGEMENT PROTOCOL

1. IF WE RECEIVE A NEONATE ACUTELY SEIZURING, WE ASSUME THE NEONATE IS IN STATUS EPILEPTICUS & MANAGED THE NEONATE USING STATUS EPILEPTICUS PROTOCOL
2. IF WE RECEIVE A NEONATE WITH HISTORY OF SEIZURE/SEIZURE LIKE EVENT, WE USE BRIGHTON COLLABORATION SCHEME TO CLASSIFY
3. WE STABILIZE THE NEONATE IF NEEDED
4. WE REVIEW NEONATE CLINICAL RECORD & DO PHYSICAL EXAMINATION USING EVALUATION PERFORMA
5. WE INITIATE BASIC WORK UP, IF NOT ALREADY DONE
6. WE PROCEED TO ADVANCE WORK UP, IF NEEDED
7. WE CORRECT METABOLIC DISTURBANCE , & LOWERS TEMPERATURE IF PRESENT
8. IF THERE IS NO HYPOGLYCEMIA OR ELETROLYTES DERANGEMENT, WE START ANTI-SEIZURE MEDS
9. WE USE PHENOBARBITONE AS FIRST LINE DRUG, IF AVAILABLE
10. WE ADD LEVETIRACETAM IF PHENOBARBITONE FAILED IN ADEQUETE DOSE, IN PATIENT WITH CARDIAC ISSUE
11. WE ADD PHYNETION OR CARBAMAZEPINE IF PHENOBARBITONE FAILED IN ADEQUETE DOSAGE & PATIENT IS SUSPECTED TO HAVE CHANNALOPATHY(POSITIVE FAMILY HISTORY)
12. WE ADD TOPERAMATE OR RIVOTRIL AS 3RD LINE DRUGS IF THE ABOVE COMBINATION FAILED
13. WE STOP ANTI-SEIZURE MEDICINE ON 28TH DAY OF NEONATAL LIFE IF;

I-EEG IS REPORTED AS NORMAL

II-THERE IS NO SUSPICION OF NEONATAL ONSET-EPILEPSY

III- NEONATE IS ON NO MORE THAN TWO ANTI-SEIZURE MEDICINE

NEONATAL STATUS EPILEPTICUS MANAGEMENT PROTOCOL

1. WHEN A NEONATE IS RECEIVED IN OUR CENTER WITH SEIZURING, WE ASSUME THE SEIZURE AS PROVOKED UNLESS IT IS ALREADY DIAGNOSED AS UNPROVOKED
2. WE ASSUME THE NEONATE IN STATUS EPILEPTICUS
3. WE STABILIZE THE NEONATE WITH ABC APPROACH
4. WE CLASSIFY THE SEIZURE USING BRIGHTON COLLABORATION SCHEME
5. WE DRAW BLOOD FOR BASIC WORK UP
6. WE USE IV PHENOBARBITONE AS FIRST LINE DRUG IF AVAILABLE OTHERWISE LEVETIRACETAM
7. WE USE MIDAZOLAM & PHYNETION AS SECOND LINE DRUGS
8. WE RUN MIDAZOLAM ± PHYNETION IN INFUSION IF NEEDED
9. IF STILL SEIZURES NOT UNDER CONTROL OR PATIENT WENT FREQUENTLY INTO STATUS EPILEPTICUS OR THERE ARE CLINICAL FEATURES OR EEG CHARACTERISTICS OF PYRIDOXINE DEPENDENT SEIZURES THEN WE SEND PATIENT TO TERTIARY CARE FOR PYRIDOXINE CHALLENGE TEST
10. IF WE SUSPECT HIE-II & THE NEONATE IS CANDIDATE FOR THERAPEUTIC HYPOTHERMIA, WE SEND PATIET TO TERTIARY CARE
11. WE USE THESE ANTI-SEIZURE MEDICINE IN FOLLOWING DOSAGES

TABLE-2

MEDICINE	LOADING DOSE	MAINTENANCE DOSE	RATE OF INFUSION
PHENOBARBITAL	20mg/kg, 2ND DOSE 10-20mg/kg IF NEEDED	5mg/kg/day BID	
LEVETIRACETAM	40mg/kg 2ND DOSE 20mg/kg IF NEEDED	40-60mg/kg/day BID/TID	
PHENYTION	20mg/kg over 30 min	5mg/kg/day BID	
MIDAZOLAM	0.05-0.15mg/kg		1µg/kg/min can be increased in steps of 1µg/kg/min up to max; 5µg/kg/min
LIDOCAINE	2mg/kg over 10 min		7mg/kg/h for ~4h then 3.5mg/kg/h for ~12h then 1.75mg/kg/h for ~12hr then stop

PYRIDOXINE CHALLENGE TEST: This test should be done in neonatal ICU set up as sudden apnea is possible complication, therefore, strict cardiopulmonary monitoring is needed. Additionally test should be done under EEG monitoring & response should be documented via EEG. Pyridoxal phosphate is preferred over pyridoxine. Measurement of SERUM pipecolic acid & alpha-aminoadipic acid semialdehyde(should be elevated) as well as simultaneous CSF-pyridoxal phosphate (should be decreased), should be ordered before iv trial

LOADING DOSE: 100-200mg pyridoxine/ pyridoxal phosphate(PLP) iv stat.

FOLLOWING DOSES: 30mg/kg/day iv bid for 5 days(IF suspicion is high, a 6-weeks oral trial of 100-200mg/day is recommended before documenting the response as NEGATIVE)

MAINTENANCE DOSE: IF response is documented as POSITIVE, a life long lengthy oral course of pyridoxine 100mg/day plus folinic acid or 15-60mg/kg/day pyridoxal phosphate is recommended

1.inj BEVIDOX 100mg pyridoxine/3ml
2. inj VIBSIX 300mg pyridoxine/3ml
3. inj pyridoxime 100mg/2ml
4.Tab VITA-6 50mg

SEIZURE LOG:

SEIZURE #	DATED	TIMING	DURATION	TERMINATED	STEROTYPE	PROBABLE TYPE	REMARKS

PATIENT MANAGEMENT CHART

1. PATIENT NAME:...

2. G/NAME:...

3. MR NO:...

VISIT DATE	WEIGHT	DISEASE STATUS	DRUG	TRADE NAME	FORM	STRENGHT	DOSE	ROUTE	REGIMEN

PATIENT MANAGEMENT CHART

1. PATIENT NAME:...

2. G/NAME:...

3. MR NO:...

VISIT DATE	WEIGHT	DISEASE STATUS	DRUG	TRADE NAME	FORM	STRENGHT	DOSE	ROUTE	REGIMEN

BRIGHTON COLLABORATION NEONATAL SEIZURES CERTAINITY LEVELS

TABLE-4

LEVELS OF DIAGNOSTIC CERTAINTY			
LEVEL		DEFINITION	COURSE OF ACTION
LEVEL-1	DEFINITE SEIZURE	SUSPECTED SEIZURE WITH CONTINUOUS EEG CORRELATE	TREAT
LEVEL-2	PROBABLE SEIZURE	SUSPECTED SEIZURE WITH AUGMENTED EEG CORRELATE OR CLINICALLY ASSESSED FOCAL TONIC/CLONIC SEIZURE	TREAT
LEVEL-3	POSSIBLE SEIZURE	CLINICAL SEIZURE OTHER THAN FOCAL CLONIC/TONIC	CONSIDER TREATMENT
LEVEL-4	SUSPECTED SEIZURE	INSUFFICIENT EVIDENCE TO MEET SEIZURE CRITERIA	DO NOT TREAT
LEVEL-5	NOT A SEIZURE	MOVEMENT DETERMINED BY EGG NOT TO BE A SEIZURE	DO NOT TREAT

NOTE: IF EEG IS NOT AVAILABLE, THE CLINICIAN CAN RELY ON LEVELS 2, 3 & 4,, DECIDING WHETHER AN EVENT IS A SEIZURE SOLELY ON THE BASIS OF CLINICAL SEMIOLOGY. IN SEIZURES CLASSIFICATION IT IS THE BEGINNING WHICH IS IMPORTATN, NOT THE END. FOR CLINICAL CLASSIFICATION THE OBSERVER MUST BE AN EXPERIENCE PERSONNEL. ALL NEONATAL SEIZURES ARE FOCAL SEIZURES UNLESS PROVED OTHERWISE

ILAE-2021 CLASSIFICATION

NEONATAL SEIZURES TYPE- CLASSIFICATION

TABLE-5

S#	SEIZURE TYPE		REMARKS
01	CLINICAL ONLY- SEIZURE		
02	ELECROCLINICAL SEIZURE		
	I -MOTOR SEIZURES	DESCRIPTORS	
	I-CLONIC SEIZURE	1-FOCAL 2-MULTIFOCAL 3-BILATERAL	
	II-TONIC SEIZURE	1-FOCAL 2-BILATERAL ASYMMETRIC 3-BILATERAL SYMMETRIC	
	III-MYOCLONIC SEIZURE	1-FOCAL 2-MULTIFOCAL 3-BILATERAL ASYMMETRIC 4-BILATERAL SYMMETRIC	
	IV-EPILEPTIC SPASM	1-UNILATERAL 2-BILATERAL ASYMMETRIC 3-BILATERAL SYMMETRIC	
	V- AUTOMATISM	1-UNILATERAL 2-BILATERAL ASYMMETRIC 3-BILATERAL SYMMETRIC	
	II-NON-MOTOR SEIZURES		
	I-AUTONOMIC SEIZURES		
	II-BEHAVIOR ARREST		
	III-SEQUENTIAL SEIZURE		
	IV-UNCLASSIFIED SEIZURE		
	ELECTROGRAPHIC- ONLY SEIZURE		

NEONATAL EPILEPSY SYNDROMES CLASSIFICATION

TABLE-6

S#	EXCLUSIVE NEONATAL EPILEPSIES (ALTHOUGH ONSET CRITERIA IS DIFFICULT TO SATISFY)
01	SELF-LIMITED EPILEPSIES
	I-SELF LIMITED NEONATAL EPILEPSY(SeLNE)
	II-SELF LIMITED FAMILIAL NEONATAL-INFANTILEEPILEPSY(SeLFNIE)
02	DEVELOPMENTAL & EPILEPTIC ENCEPHALOPATHIES(DEE)
	I-KCNQ2-DEE
	II-PYRIDOXINE-DEPENDANT-DEE
	III-PYRIDOXINE 5-PHOSPHATE DEFICIENCY-DEE
	IV-OTOHARA SYNDROME(EARLY INFANTILE DEVELOPMENTAL & EPILEPTIC ENCEPHALOPATHY)

RISK FACTORS OF NEONATAL SEIZURES

TABLE-7

S#	CATEGORY	RISK FACTORS
01	MATERNAL INFLUENCES	1-MATERNAL AGE 2-NULLIPARITY 3-DIABETES 4-SUBSTANCE ABUSE 5-LACK OF ANTENATAL SCREENING 6-OTHERS
02	PERINATAL FACTORS	1-FOETAL DISTRESS 2-PLACENTAL INSUFFICIENCY/ABRUPTION 3-CORD PROLAPSE 4-PROLONG SECOND STAGE OF LABOR 5-PROM 6-OLIGOHYDRAMNIOS 7-PERIPARTUM FEVER/CHORIOAMNIONITIS 8-OTHERS
03	NEONATE CHARACTERISTICS	1-LOW BIRTH WEIGHT 2-LOW APGARS 3-HYPOGLYCEMIA 4-MALE SEX 5-PREMATURITY 6-POSTMATURITY 7-CONGENITAL HEART DISEASE 8-OTHERS
04	FAMILY HISTORY	1-SEIZURE DISORDER 2-METABOLIC DISORDER 3-BLEEDING/COAGULATION DISORDER 4-OTHERS

ETIOLOGY OF NEONATAL SEIZURES

TABLE-8

S#	CAUSE OF SEIZURE	REMARKS	DESCRIPTION
1	HYPOXIC ISCHEMIC ENCEPHALOPATHY(50-60%)		GENERALLY OCCUR WITHIN 12-24H AFTER BIRTH
2	STRUCTURAL(10-20%) I-VASCULAR 1-INTRACRANIAL HAEMORRHAGE i-SUBDURAL ii-SUBARACHNOID iii-GERMINAL MATRIX iv-INTRAVENTRICULAR 2-ISCHEMIC STROKE 3-CONGENITAL VASCULAR MALFORMATION II-BRAIN MALFORMATION 1-FOCAL 2-DIFFUSE		FOCAL: AGENESIS OF CORPUS CALLOSUM, DANDY-WALKER MALFORMATION VENOUS MALFORMATIONS DIFFUSE:HOLOPROSENCEPHALY, LISSENCEPHALY POLYMICROGYRIA
3	INFECTIUOS(5-10%) 1-BACTERIAL 2-VIRAL 3-CONGENITAL TORCHES 4-FUNGAL		SEIZURES OFTEN PROLONG & DIFFICULT TO TREAT
4	GENETIC		
5	METABOLIC (~5%)		
6	NEONATAL EPILEPSY SYNDROME (~1%)		FAMILY HX MAY BE POSITIVE
7	DRUG INTOXICATION/WITHDRAWL (~1%)		COMMONLY TCA, BENZODIAZEPINES, BARBITURATES
8	UNKNOWN		

ANTI-SEIZURE DRUGS (ORAL)

TABLE-9

S #	MEDICINE NAME	TRADE NAME	FORMULATION	STRENGTH	DAILY DOSE	MAX; DAILY DOSE	REGIMEN
1	PHENOBARBITONE	DEBRITONE	SYRUP	20mg/5ml	5-8mg/kg	40mg	BID
2	PHENOBARBITONE	PHENOBARBITONE	TABLET	30mg	5-8mg/kg	40mg	BID
3	PHYNETION	EPITION	SYRUP	30mg/5ml	5-20mg/kg	300mg	BID
4	LEVETIRACETAM	LERACE	SYRUP	100mg/ml	10-30mg/kg	50mg/kg	BID
5	CARBAMAZEPINE	SEIZUNIL	SYRUP	100mg/5ml	10-35mg/kg	35mg/kg	BID,TID,QID
6	CLONAZEPAM	RIVOTRIL	DROPS	0.25% DROPS	0.01-0.03mg/kg	0.2mg/kg	TID,QID

ANTI-SEIZURE DRUGS (INJECTABLES)

TABLE-10

S#	MEDICINE NAME	TRADENAME	FORMULATION	STRENGTH	DAILY DOSE	MAX;DAILY DOSE	REGIMEN
1	PHENOBARBITAL	P-BAR	INJECTION	200mg/ml	20mg/kg	45mg/kg	LOADING
2	PHENYTION	EPIGRAN	INJECTION	250mg/ml	20mg/kg	45mg/kg	LOADING
3	LEVETIRACETAM	LERACE	INJECTION	500mg/5ml	20mg/kg		LOADING
4	MIDAZOLAM	DORMICUM	INJECTION	5mg/5ml	0.15mg/kg		LOADING

ANTI-SEIZURE DRUGS (INFUSION)

INJ=DORMICUM=5mg/5ml
INFUSION RATE 1-2mcg/kg/min OR 1-2mcg /kg/hour
NOW IF CHILD WEIGHT IS 10kg & rate 2mcg/kg/min then
10x2/min=20mcg OR 10x2x60/hour=1200mcg/hour OR 1.2mg/hour
NOW PUT 5ml dormicum in 100 ml Normal Saline then;
1.2x100/5mg=22ml/hour

DEFINITIONS

DEFINITIONS

1. ***SEIZURE:*** A seizure is currently defined as a transient occurrence of signs/±symptoms due to abnormal excessive or synchronous neuronal activity in the brain

2. ***SEIZURE SEMIOLOGY***: Semiology is the description of signs & symptoms associated with an ictal event & is valuable in localizing the epileptogenic zone

3. ***EPILEPSY:*** A Seizure does not necessarily mean that a person has epilepsy; for epilepsy to be diagnosed anyone of the following criteria must be satisfied

    a-at least two unprovoked seizures occurring >24 hours apart

    b-a diagnosis of epilepsy syndrome

    c- one unprovoked seizure and a probability of further seizure similar to the general recurrence risk after two unprovoked seizures (~50%)

4. ***EPILEPSY SYNDROME:*** A characteristic cluster of clinical & EEG features,often supported by specific etiological findings

5. **EEG BASED DEFINITIONS:**

    I-ELECTROGRAPHIC NEONATAL SEIZURE: THE ACN SOCIETY HAS RECENTLY DEFINED AN ELECTROGRAPHIC NEONATAL SEIZURE AS a sudden, abnormal eeg event, defined by repetitive & evolving pattern with a minimum 2µv peak-to-peak voltage & duration of at least 10 seconds. evolving pattern is defined as unequivocal evolution in frequency, voltage, morphology or location e.g. increasing amplitude & decreasing frequency of discharges over time

    II- THE ILAE-2021 TASKFOCE DEFINED NEONATALSEIZURE AS an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning & end. the duration is not defined but has to be sufficient to demonstrate evolution in frequency & morphology of the discharges & needs to be long enough to allow recognition of onset, evolution & resolution of an abnormal discharge

    III-***SEIZURE BURDEN***:Ictal electrographic activity in a given period of eeg recording & expressed as summed electrographic seizure seconds.(electrographic seizure seconds in a given period). it has been suggested that seizure burden >30s/hour should be considered as indication for start of treatment.

IV- ***SEIZURE FREQUENCY:*** Number of seizures in a given period regardless of duration.

V-NEONATAL STATUS EPILEPTICUS: A continuous seizure lasting at least thirty minutes or A series of seizures whose total duration exceeds 50% of a given epoch on eeg